Hair-bearing human skin generated entirely from pluripotent stem cells.

Journal: Nature

Publication Year: 2020

Authors: Jiyoon Lee, Cyrus C Rabbani, Hongyu Gao, Matthew R Steinhart, Benjamin M Woodruff, Zachary E Pflum, Alexander Kim, Stefan Heller, Yunlong Liu, Taha Z Shipchandler, Karl R Koehler

PubMed link: 32494013

Funding Grants: CIRM 2.0 Bridges Training Program

Public Summary:
The skin is a multi-layered organ equipped with appendages (i.e. follicles and glands) critical for regulating bodily fluid retention and temperature, guarding against external stresses, and mediating touch and pain sensation1,2. Reconstruction of appendage-bearing skin in cultures and in bioengineered grafts remains an unmet biomedical challenge3–9. Here, we report an organoid culture system that generates complex skin from human pluripotent stem cells. We use step-wise modulation of the TGFβ and FGF signalling pathways to co-induce cranial epithelial cells and neural crest cells within a spherical cell aggregate. During 4–5 months incubation, we observe the emergence of a cyst-like skin organoid composed of stratified epidermis, fat-rich dermis, and pigmented hair follicles equipped with sebaceous glands. A network of sensory neurons and Schwann cells form nerve-like bundles that target Merkel cells in organoid hair follicles, mimicking human touch circuitry. Single-cell RNA-sequencing and direct comparison to foetal specimens suggest that skin organoids are equivalent to human facial skin in the second-trimester of development. Moreover, we show that skin organoids form planar hair-bearing skin when grafted on nude mice. Together, our results demonstrate that nearly complete skin can self-assemble in vitro and be used to reconstitute skin in vivo. We anticipate skin organoids will be foundational to future studies of human skin development, disease modelling, or reconstructive surgery.

Scientific Abstract:
The skin is a multilayered organ, equipped with appendages (that is, follicles and glands), that is critical for regulating body temperature and the retention of bodily fluids, guarding against external stresses and mediating the sensation of touch and pain(1,2). Reconstructing appendage-bearing skin in cultures and in bioengineered grafts is a biomedical challenge that has yet to be met(3-9). Here we report an organoid culture system that generates complex skin from human pluripotent stem cells. We use stepwise modulation of the transforming growth factor beta (TGFbeta) and fibroblast growth factor (FGF) signalling pathways to co-induce cranial epithelial cells and neural crest cells within a spherical cell aggregate. During an incubation period of 4-5 months, we observe the emergence of a cyst-like skin organoid composed of stratified epidermis, fat-rich dermis and pigmented hair follicles that are equipped with sebaceous glands. A network of sensory neurons and Schwann cells form nerve-like bundles that target Merkel cells in organoid hair follicles, mimicking the neural circuitry associated with human touch. Single-cell RNA sequencing and direct comparison to fetal specimens suggest that the skin organoids are equivalent to the facial skin of human fetuses in the second trimester of development. Moreover, we show that skin organoids form planar hair-bearing skin when grafted onto nude mice. Together, our results demonstrate that nearly complete skin can self-assemble in vitro and be used to reconstitute skin in vivo. We anticipate that our skin organoids will provide a foundation for future studies of human skin development, disease modelling and reconstructive surgery.